#34

Docket No.: 002010137
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Eugene D. THORSETT, et al.

Application No.: 09/126,096 Group Art Unit: 1624

Filed: July 30, 1998 Examiner: D. RAO

For: COMPOUNDS WHICH INHIBIT LEUKOCYTE ADHESION MEDIATED BY VLA-4

APPELLANT'S BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P. O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

This brief is in furtherance of the Notice of Appeal, filed in this case on May 5, 2003. Note the time for filing this brief runs from May 5, 2003. See paper No. 32 in this case. A Petition requesting a three month extension of time accompanies this brief which extends the due date for filing the Brief to October 5, 2003 which is further extended to October 6, 2003 since the 5th is a Sunday.

The fees required under §1.17(f) and the required fee for the petition for extension of time for filing this brief, are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief is transmitted in triplicate.

This brief contains items under the following headings per 37 C.F.R. § 1.192:

I. Real Party In Interest

II Related Appeals and Interferences

III. Status of Claims

IV. Status of Amendments

V. Summary of Invention

VI. Issues

VII. Grouping of Claims

VIII. Arguments

IX. Claims Involved in the Appeal

Appendix A Claims

I. REAL PARTY IN INTEREST

The real parties in interest for this appeal are Elan Pharmaceuticals, Inc. (successor to the interests of Athena Neurosciences) and Wyeth, Inc. (successor to the interests of American Home Products, Inc.).

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are sixteen (16) claims pending in application.

B. Current Status of Claims

1. Claims canceled: 5, 6, 8, 9, 11, and 14
2. Claims withdrawn from consideration but not canceled: None
3. Claims pending: 1-4, 7, 10, 12, 13, and 15-22

4. Claims allowed: none

5. Claims rejected: 1-4, 7, 10, 12, 13, and 15-22

6. Claims objected to: none

C. Claims On Appeal

Claims 1-4, 7, 10, 12, 13, and 15-22 are on appeal. All of the claims on appeal appear in the Appendix A attached hereto.

IV. STATUS OF AMENDMENTS

As understood by the Applicants, all of the requested amendments have been entered. All amendments appear in the conformed claims in the Appendix A attached hereto.

V. SUMMARY OF INVENTION

The present invention is directed to novel compounds, and compositions thereof, which inhibit leukocyte adhesion and, in particular, leukocyte adhesion mediated by VLA-4. Compounds of the subject invention are detailed, for example, in the Specification, on page 5, line 13 to page 35, last line. The subject invention also includes various methods of treatment of various inflammatory diseases mediated, at least in part, by VLA-4, using the compounds and compositions of the subject invention. Said methods of treatment may be found, in the Specification, on page 24, line 5 to page 25, line 2.

VI. ISSUES

1. The only issue on appeal is whether Claims 1-4, 7, 10, 12, 13 and 15-22 are unpatentable over Claims 1-35 of U.S. Patent No. 6,492,421 under the judicially created doctrine of obviousness-type double patenting.

It is requested that this rejection be reversed.

VII. GROUPING OF CLAIMS

Claims 1-4, 7, 10, 12, 13, and 15-22 all stand or fall together.

VIII. ARGUMENTS

Relief Requested

It is requested that the rejection of Claims 1-4, 7, 10, 12, 13, and 15-22 be reversed by the Board. Applicants have repeatedly iterated the patentability of the presently claimed compounds which feature a non-naturally occurring α,α-disubstituted amino acid side chain for the naturally occurring α-substituted amino acid side chain. The Examiner has not set forth a *prima facie* case of obviousness because no credible motivation for making the claimed compounds with a reasonable expectation that they would have the properties they exhibit has been articulated. The Examiner has merely alleged that the presently claimed compounds are obvious over structurally similar compounds.

As to this argument, there simply was no motivation present at the time of the present invention to modify those structurally similar compounds to produce the presently claimed compounds. Additionally, there was no reasonable expectation that the presently claimed compounds would exhibit properties useful for treating VLA-4 associated diseases. Both are required to set forth a *prima facie* case of obviousness.

The Examiner has not articulated a credible motivation to make the claimed compounds with a reasonable expectation of success

The patent law is clear that the prior art must provide sufficient basis for an expectation of success in order for a *prima facie* case of obviousness to exist. *See, In re Merck, 800 F.2d 1091, 1097, 231 USPQ 375, 379 (Fed. Cir. 1986)* The Examiner has failed to explain why a skilled artisan would be motivated to substitute a non-naturally occurring α, α-disubstituted amino acid side

chain for the naturally occurring α-substituted amino acid side chain. The Examiner asserts on page 3, second paragraph of the Advisory Action mailed on May 23, 2003 that "[T]he reference disclosed compounds "as a whole" provide sufficient motivation to one of ordinary skill in the art to prepare the structural homologs thereof by introducing a methyl group in place of the hydrogen, with the reasonable expectation of obtaining compounds having similar properties." This is clearly afoul of the law. The law is clear that "The motivation may not be abstract, but practical, and is always related to the properties or uses one skilled in the art would expect the compound to have, if made." *See, In re Gyurik*, 201 USPQ 552 (CCPA 1979) The Examiner has failed to articulate why a skilled artisan would reasonably expect success from making such a substitution. The Examiner merely contends that "The reference compounds are taught to be useful as therapeutic agents for treatment of diseases mediated by VLA-4, which provides sufficient motivation to one of ordinary skill in the art to prepare the homologs with the expectation of obtaining compounds having similar properties." *See, Advisory Action mailed May 23, 2003, first paragraph.* Such a statement does not explain why one of ordinary skill in the art would be motivated to make an α,α-disubstituted amino acid side chain substitution for the naturally occurring α-substituted amino acid side chain with a reasonable expectation that such a substitution would produce compounds having similar properties. There is absolutely nothing in the prior art reference that would suggest the properties of the α, α-disubstituted amino acids. The Examiner has set forth a mere conclusory allegation.

Absent both motivation and a reasonable expectation of success, a *prima facie* case of obviousness is not presented. Yet, the Examiner mistakenly and afoul of the law assumes a *prima facie* case of obviousness is established and requests additional evidence of unexpected properties in order to demonstrate the patentability of the claims.

Structure alone does not dictate obviousness of chemical compounds

The structural similarity of the claimed compounds as compared to those of the prior art reference is not dispositive of patentability. It is a long held axiom of the patent law that questions of chemical obviousness cannot be decided on the basis of structure alone. *See, In re Papesch* (CCPA 1963) 315 F.2d 381, 137 USPQ 43. Moreover, whether obviousness of structure creates an inference of obviousness within the meaning of 35 USC §103, a *prima facie* showing of obviousness, or a presumption of obviousness is immaterial. Even structural obviousness alone is not a bar under 35 USC §103 to the grant of a patent to a chemical compound. *See, Comr. Pats. V. Deutsche Gold-und-Silber, etc.* (CADC 1968) 397 F.2d 656, 157 USPQ 549. The inquiry into the patentability of the presently claimed compounds must also extend to the properties that they exhibit. As set forth, *supra*, the Examiner has simply not demonstrated that those of ordinary skill in the art would expect the presently claimed compounds to be useful for treating VLA-4 related diseases.

Homology alone does not determine patentability

The Examiner says that no explanation or data refuting that the homologs would have the properties of the unsubstituted compounds of the prior art has been presented. *See, Advisory Action, first paragraph.* The mere fact that a claimed compound has an empirical formula which differs from a prior art compound by CH_2 or multiple thereof does not establish them as members of the same homologous series. *See, Ex parte Burtner et al.* (POBA 1951) 121 USPQ 345. Even if, *assuming arguendo*, the presently claimed compounds could be considered homologs to the prior art compounds, such a categorization is not dispositive of patentability. Homology is nothing more than a fact that must be considered with all other relevant facts in applying the statutory tests of obviousness. *See, In re Mills* (CCPA 1960) 281 F.2d 218, 126 USPQ 513. The courts have clearly

expressed that homology should not be automatically equated with *prima facie* obviousness. *See, In re Langer et al.* (CCPA 1972) 465 F.2d 896, 175 USPQ 169.

The Board has applied similar analysis to other subject matter

The final Office Action mailed on February 4, 2003 (Paper No. 29) asserts that Applicants prior reliance on *In re Coe*s, 81 USPQ 369 (CCPA 1949), *In re Langer* 175 USPQ 169 (CCPA 1972).and *In re Lalu*, 223 USPQ 1257 (CAFC 1984).is misplaced. Yet, with respect to each case, the Examiner's arguments are incorrect.

In re Coes held that the prior art ether compound:

$$ClCH_2CH_2OCH_2CH_2OCH_2CH_2Cl$$

created an unrebutted *prima facie* case of obviousness against the claimed acetal compound:[1]

$$ClCH_2CH_2OCH_2OCH_2CH_2Cl$$

because the prior art was a homologue of the claimed compound differing only by a $-CH_2-$unit (i.e., $-CH_2CH_2$ versus $-CH_2-$) and because acetals have similar chemical properties to ethers.[2] In short, the structural similarity was insufficient alone to establish a *prima facie* case of obviousness. More was required. It was because acetals were known in the prior art to have similar chemical properties to ethers that a *prima facie* case of obviousness was established. In the instant case, the Examiner has not established that α,α-disubstituted amino acids of this invention were known to have the same chemical properties of α-substituted amino acids. Applicants submit that they do not.

As set forth, *supra, In re Langer* held that obviousness must be established against the invention "as a whole" and that rules such as homology cannot, by themselves, be used as a basis to render a *prima facie* case of obviousness.[3] The Examiner is mistaken in asserting in the final Office

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[1] *In re Coes*, 81 USPQ at 371, (concluding that the claimed compound was obvious and in the penultimate paragraph at page 371 concluding that the data in the application did not substantiate patentability (i.e., rebutted the *prima facie* case)).
[2] *Id.* page 371.
[3] *In re Langer* 175 USPQ 169 (CCPA 1972) at 171.

Action that because *In re Langer* was limited to hindered amines versus unhindered amines, the holding of the case is not germane to the present issues. The court in *In re Langer* held that it is important to show obviousness to the invention "as a whole" and thus viewed the Applicants invention as the use of sterically hindered amines as opposed to unhindered amines.[4] The same analysis in the present case necessitates a determination of whether the claimed α,α-disubstituted amino acids, when viewed as a whole, are obvious over the α-substituted amino acids of the '421 patent.[5]

The court of *In re Lalu* held that an obviousness analysis requires an inquiry as to whether anything in the prior art reference suggests the properties of the claimed compounds.[6] Hence, *In re Lalu* is just one more instance where the properties of the claimed compounds in addition to the structure was considered in determining patentability.

The final Office Action also relies upon *In re Deuel* to support the allegations of obviousness.[7] Applicants maintain that such reliance is misplaced. Specifically, *In re Deuel* addresses the question of whether cDNA molecules that encode heparin-binding growth factors are obvious over references disclosing known methods of making the molecules.[8] In deciding that case, the court recited with approval language directly from *In re Lalu* that "The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compounds."[9] Such an analysis is contrary to any formulaic rules and, accordingly, supports Applicants' position that a mere assertion of homology is insufficient to create a *prima facie* case of obviousness absent any evidence that such homology would motivate the skilled artisan to make the necessary modifications.

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[4] *In re Langer* 175 USPQ 169 (CCPA 1972).
[5] This invention, as a whole, includes the α,α-disubstituted amino acids per se, pharmaceutical compositions comprising these compounds as well as methods of use using these compounds.
[6] *In re Lalu*, 223 USPQ 1257 (CAFC 1984) at 1260.
[7] *In re Deuel*, 34 USPQ.2d 1210 (CAFC 1995).
[8] *Id.* at 1214.
[9] *Id.* at 1215.

The Board has recognized the patentability of novel compounds in circumstances similar to those presently at issue

The Board of Appeals refused to use homology as a reason to deny the patentability of compounds having an alkylene group between a ring and ester function of the prior art compound. *See, Ex parte Biel* (POBA 1958) 124 USPQ 109; *Ex parte Goonewardene et al.* (POBA 1968) 160 USPQ 287. Thus, inserting a CH_2 group between the CO and COOH of a –CO-COOH group of the prior art compound was held by this Board to be sufficient structural difference to render the claimed compounds patentable even without a showing of unexpected properties. This conclusion that the claims were patentable was reached in spite of the fact that the claimed compounds might be regarded as "homologs" of the prior art compounds in a broad sense. *See, Ex parte Burtner et al.* (POBA 1950) 89 USPQ 547.

Compounds in which a thienyl group and a carboxy group were attached to the same ring carbon atom of a cyclohexane ring were held not to be homologs of prior art compounds in which thienyl, carboxy and cyclohexyl groups were attached to the same carbon atom. In this instance, the Board realized the difference in properties resulting from the structural change was not predictable from the homology. *See, Ex parte Tilford et al.* (POBA 1953) 121 USPQ 347.

No showing of unexpectedly superior results is necessary

The Examiner says that no data or arguments have been submitted sufficient to establish unexpected properties of the claimed compounds. *See, Advisory Action, paragraphs 1 and 2.* This Board has previously held that even though the claimed compounds and prior art compounds differ structurally by a CH_2 group, unless their equivalency or close relationship would have been recognized by those skilled in the art, a showing of unobvious or unexpected properties need not be

made to establish patentability. *See, Ex parte Thompson* (POBA 1954) 119 USPQ 254; *In re Shetty* (CCPA 1977) 556 F.2d 81, 195 USPQ 753.

Even in view of this, Applicants have submitted evidence of the non-equivalence between α-substituted amino acids and α,α-disubstituted amino acids. Salgado, *et al.*, teaches that peptides containing α,α-disubstituted amino acids confer conformational rigidity and resistance to enzymatic hydrolysis as compared to peptides containing α-monosubstituted amino acids.[10] This is clearly a non-equivalent property of the presently claimed compounds as compared to the prior art. Contrary to the Examiner's position, it is immaterial whether Salgado *et al.* specifically compare the conformational rigidity of disubstituted amino acids with monosubstituted amino acids. The property exists and no such comparison is required to prove it exists. Further, the Examiner offers no more than speculation to rebut this property alleging that "[t]his very rigidity of the cyclopropane may be contributing to the conformational restrictions discussed in the reference." *See, Advisory Action, page 3, second paragraph.* Unsupported speculation cannot serve as a basis for establishing obviousness under 35 U.S.C. §103. Reasonable certainty is required to render a property expected.

IX. CLAIMS INVOLVED IN THE APPEAL

A copy of the claims involved in the present appeal is attached hereto as Appendix A.

[10] Salgado, et al., *Enzyme-mediated Synthesis of (IS)-1-amino-2,2-dimethylcyclopropane-l-Carboxylic acid*, FOURTH INTERNATIONAL ELECTRONIC CONFERENCE ON SYNTHETIC ORGANIC CHEMISTRY, September 2000 (available at http://www.unibas.ch/mdpi/ecsoc-4/a0024.htm).

CONCLUSION

Appellants respectfully request that the Board of Patent Appeals and Interferences reverse the rejection of Claims 1-4, 7, 10, 12, 13 and 15-22 as unpatentable over Claims 1-35 of U.S. Patent No. 6,492,421 under the judicially created doctrine of obviousness-type double patenting. For the reasons noted herein, Appellants maintain that a *prima facie* case of obviousness has not been established against the claimed invention.

Dated: October 6, 2003

Respectfully submitted,

By _____

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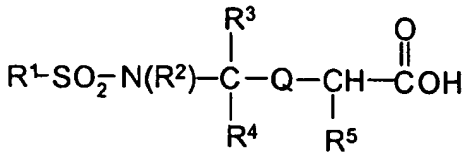
APPENDIX A

Claims Involved in the Appeal of Application Serial No. 09/126,096

1. (Four times amended): A compound of formula I:



I

where

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a heterocyclic or a substituted heterocyclic group selected from the group consisting of thiazolidinyl, piperidinyl and pyrrolidinyl wherein said substituted heterocyclic group consists of from 1 to 2 substituents selected from the group consisting of fluoro, methyl, hydroxyl, amino, phenyl, thiophenyl and thiobenzyl;

R^4 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^5 is selected from the group consisting of isopropyl, $-CH_2X$ and =CH-X where X is selected from the group consisting of:

hydrogen,

hydroxyl,

acylamino,

alkyl,

alkoxy,

aryloxy,

aryl,

aryloxyaryl,

carboxyl,

carboxylalkyl,

carboxyl-substituted alkyl,

carboxyl-cycloalkyl,

carboxyl-substituted cycloalkyl,

carboxylaryl,

carboxyl-substituted aryl,

carboxylheteroaryl,

carboxyl-substituted heteroaryl,

carboxylheterocyclic,

carboxyl-substituted heterocyclic,

cycloalkyl,

substituted alkyl

substituted alkoxy,

substituted aryl,

substituted aryloxy,

substituted aryloxyaryl,

substituted cycloalkyl,

heteroaryl,

substituted heteroaryl,

heterocyclic,

and substituted heterocyclic;

wherein substituted aryl refers to aryl groups substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heterocyclic, substituted heterocyclic, oxycarbonylamino, oxythiocarbonylamino, $-S(O)_2$-alkyl, $-S(O)_2$-substituted alkyl, $-S(O)_2$- cycloalkyl, $-S(O)_2$-substituted cycloalkyl, $-S(O)_2$-alkenyl, $-S(O)_2$-substituted alkenyl, $-S(O)_2$- aryl, $-S(O)_2$-substituted aryl, $-S(O)_2$-heteroaryl, $-S(O)_2$-substituted heteroaryl, $-S(O)_2$-heterocyclic, $-S(O)_2$-substituted heterocyclic, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, -OSO2-NRR where R is hydrogen or alkyl, $-NRS(O)_2$- alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino,

mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups selected from the group consisting of Boc, Cbz, and formyl or substituted with $-SO_2NRR$ where R is hydrogen or alkyl; and

substituted heteroaryl refers to heteroaryl groups substituted with from 1 to 3 substituents selected of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heterocyclic, substituted heterocyclic, oxycarbonylamino, oxythiocarbonylamino, $-S(O)_2$-alkyl, $-S(O)_2$-substituted alkyl, $-S(O)_2$- cycloalkyl, $-S(O)_2$-substituted cycloalkyl, $-S(O)_2$-alkenyl, $-S(O)_2$-substituted alkenyl, $-S(O)_2$-aryl, $-S(O)_2$-substituted aryl, $-S(O)_2$-heteroaryl, $-S(O)_2$-substituted heteroaryl, $-S(O)_2$-heterocyclic, $-S(O)_2$-substituted heterocyclic, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2NRR$ where R is hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted

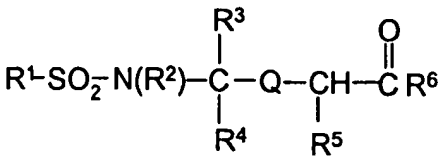
alkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substituted aryl, -NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups selected from the group consisting of Boc, Cbz, and formyl or substituted with $-SO_2NRR$ where R is hydrogen or alkyl;

with the proviso that when R^5 is =CH-X then (H) is removed from the formula and X is not hydroxyl;

Q is -C(X')NR^7- wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X' is selected from the group consisting of oxygen and sulfur;

or pharmaceutically acceptable salts thereof.

2. (Four times amended): A compound of formula IA below:



IA

where

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a heterocyclic or a substituted heterocyclic group selected from the group consisting of thiazolidinyl, piperidinyl and pyrrolidinyl wherein said substituted heterocylcic group consists of from 1 to 2 substituents selected from the group consisting of fluoro, methyl, hydroxyl, amino, phenyl, thiophenyl and thiobenzyl;

R^4 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^5 is selected from the group consisting of isopropyl, $-CH_2X$ and $=CH-X$ where X is selected from the group consisting of:

hydrogen,

hydroxyl,

acylamino,

alkyl,

alkoxy,

aryloxy,

aryl,

aryloxyaryl,

carboxyl,

carboxylalkyl,

carboxyl-substituted alkyl,

carboxyl-cycloalkyl,

carboxyl-substituted cycloalkyl,

carboxylaryl,

carboxyl-substituted aryl,

carboxylheteroaryl,

carboxyl-substituted heteroaryl,

carboxylheterocyclic,

carboxyl-substituted heterocyclic,

cycloalkyl,

substituted alkyl

substituted alkoxy,

substituted aryl,

substituted aryloxy,

substituted aryloxyaryl,

substituted cycloalkyl,

heteroaryl,

substituted heteroaryl,

heterocyclic,

and substituted heterocyclic;

wherein substituted aryl refers to aryl groups substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl,

guanidino, guanidinosulfone, halo, nitro, heterocyclic, substituted heterocyclic, oxycarbonylamino, oxythiocarbonylamino, -$S(O)_2$-alkyl, -$S(O)_2$-substituted alkyl, -$S(O)_2$- cycloalkyl, -$S(O)_2$-substituted cycloalkyl, -$S(O)_2$-alkenyl, -$S(O)_2$-substituted alkenyl, -$S(O)_2$-aryl, -$S(O)_2$-substituted aryl, -$S(O)_2$-heteroaryl, -$S(O)_2$-substituted heteroaryl, -$S(O)_2$-heterocyclic, -$S(O)_2$-substituted heterocyclic, -$OS(O)_2$- alkyl, -$OS(O)_2$- substituted alkyl, -$OS(O)_2$-aryl, -$OS(O)_2$-substituted aryl, -$OS(O)_2$-heteroaryl, -$OS(O)_2$-substituted heteroaryl, -$OS(O)_2$-heterocyclic, -$OS(O)_2$-substituted heterocyclic, -OSO_2-NRR where R is hydrogen or alkyl, -$NRS(O)_2$-alkyl, -$NRS(O)_2$-substituted alkyl, -$NRS(O)_2$-aryl, -$NRS(O)_2$-substituted aryl, -$NRS(O)_2$-heteroaryl, -$NRS(O)_2$-substituted heteroaryl, -$NRS(O)_2$-heterocyclic, -$NRS(O)_2$-substituted heterocyclic, -$NRS(O)_2$-NR-alkyl, -$NRS(O)_2$-NR-substituted alkyl, -$NRS(O)_2$-NR-aryl, -$NRS(O)_2$-NR-substituted aryl, -$NRS(O)_2$-NR-heteroaryl, -$NRS(O)_2$- NR-substituted heteroaryl, -$NRS(O)_2$-NR-heterocyclic, -$NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups selected from the group consisting of Boc, Cbz, and formyl or substituted with -SO_2NRR where R is hydrogen or alkyl; and

substituted heteroaryl refers to heteroaryl groups substituted with from 1 to 3 substituents selected of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-

substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heterocyclic, substituted heterocyclic, oxycarbonylamino, oxythiocarbonylamino, $-S(O)_2$-alkyl, $-S(O)_2$-substituted alkyl, $-S(O)_2$- cycloalkyl, $-S(O)_2$-substituted cycloalkyl, $-S(O)_2$-alkenyl, $-S(O)_2$-substituted alkenyl, $-S(O)_2$-aryl, $-S(O)_2$-substituted aryl, $-S(O)_2$-heteroaryl, $-S(O)_2$-substituted heteroaryl, $-S(O)_2$-heterocyclic, $-S(O)_2$-substituted heterocyclic, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where R is hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$- substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups selected from the group consisting of Boc, Cbz, and formyl or substituted with $-SO_2NRR$ where R is hydrogen or alkyl;

with the proviso that when R^5 is =CH-X then (H) is removed from the formula and X is not hydroxyl;

R^6 is selected from the group consisting of amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, or substituted aryl, $-NH(CH_2)_pCOOY$ where *p* is an integer of from 1 to 8 and Y is as defined above, $-OCH_2NR^9R^{10}$ where R^9 is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and R^{10} is selected from the group consisting of hydrogen and $-CH_2COOR^{11}$ where R^{11} is alkyl, and $-NHSO_2Z$ where Z is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

Q is $-C(X')NR^7-$ wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X' is selected from the group consisting of oxygen and sulfur;

or pharmaceutically acceptable salts thereof

with the proviso that

when R^1 is *p*-methylphenyl, R^2 and R^3 are joined together with the nitrogen atom pendent to R^2 and the carbon atom pendent to R^3 to form a pyrrolidinyl ring, R^4 is methyl, R^5 is *p*-hydroxybenzyl then R^6 is not *t*-butoxy.

3. (Original): The compound according to Claims 1 or 2 wherein R^1 is selected from the group consisting of aryl, substituted aryl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl.

4. (Original): The compound according to Claims 1 or 2 wherein R^1 is selected from the group consisting of 4-methylphenyl, methyl, benzyl, *n*-butyl, 4-chlorophenyl, 1-naphthyl, 2-naphthyl, 4-methoxyphenyl, phenyl, 2,4,6-trimethylphenyl, 2-(methoxycarbonyl)phenyl, 2-

carboxyphenyl, 3,5-dichlorophenyl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl, 3,4-dimethoxyphenyl, 4-($CH_3C(O)NH$-)phenyl, 4-trifluoromethoxyphenyl, 4-cyanophenyl, isopropyl, 3,5-di-(trifluoromethyl)phenyl, 4-*t*-butylphenyl, 4-tbutoxyphenyl, 4-nitrophenyl, 2-thienyl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl, phenethyl, 1-N-methylimidazol-4-yl, 4-bromophenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-[$CH_3SC(=NH)$]phenyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methyl-4-pyrazolyl, 2-thiazolyl, 5-methyl-1,3,4-thiadiazol-2-yl, 4-[$H_2NC(S)$]phenyl, 4-aminophenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,5-difluorophenyl, pyridin-3-yl, pyrimidin-2-yl, and 4-(3'-dimethylamino-*n*-propoxy)-phenyl.

7. (Once amended): The compound according to Claims 1 or 2 wherein R^2 and R^3 together with the nitrogen atom bound to R^2 substituent and the carbon bound to the R^3 substituent form a substituted heterocyclic ring.

10. (Original): The compound according to Claim 1 or 2 wherein R^4 is selected from the group consisting of methyl, ethyl and phenyl.

12. (Once amended): The compound according to Claims 1 or 2 wherein R^5 is selected from the group consisting of 4-methylbenzyl, 4-hydroxybenzyl, 4-methoxybenzyl, 4-*t*-butoxybenzyl, 4-benzyloxybenzyl, 4-[ø-$CH(CH_3)O$-]benzyl, 4-[ø-CH(COOH)O-]-benzyl, 4-[$BocNHCH_2C(O)NH$-]benzyl, 4-chlorobenzyl, 4-[$NH_2CH_2C(O)NH$-]benzyl, 4-carboxybenzyl, 4-[$CbzNHCH_2CH_2NH$-]benzyl, 3-hydroxy-4-(ø-OC(O)NH-)benzyl, 4-[$HOOCCH_2CH_2C(O)NH$-]benzyl, benzyl, 4-[-C(O)NH-]benzyl, 3-carboxybenzyl, 4-iodobenzyl, 4-hydroxy-3,5-diiodobenzyl, 4-hydroxy-3-iodobenzyl, ø-CH_2CH_2, 4-nitrobenzyl, 2-carboxybenzyl, 4-[dibenzylamino]-benzyl, 4-[(1'-cyclopropylpiperidin-4'-yl)-C(O)NH-]benzyl, 4-[-$NHC(O)CH_2NHBoc$]benzyl, 4-carboxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-[-$NHC(O)CH(CH_3)NHBoc$]benzyl, 4-[-$NHC(O)CH(CH_2ø)NHBoc$]-

benzyl, isobutyl, methyl, 4-[$CH_3C(O)NH$-]benzyl, -CH_2-(3-indolyl), *n*-butyl, *t*-butyl-$OC(O)CH_2$-, *t*-butyl-$OC(O)CH_2CH_2$-, $H_2NC(O)CH_2$-, $H_2NC(O)CH_2CH_2$-, BocNH-$(CH_2)_4$-, *t*-butyl-OC(O)-$(CH_2)_2$-, $HOOCCH_2$-, $HOOC(CH_2)_2$-, $H_2N(CH_2)_4$-, isopropyl, (1-naphthyl)-CH_2-, (2-naphthyl)-CH_2-, (2-thiophenyl)-CH_2-, ø-CH_2-$OC(O)NH$-$(CH_2)_4$-, cyclohexyl-CH_2-, benzyloxy-CH_2-, $HOCH_2$-, 5-(3-N-benzyl)imidazolyl-CH_2-, 2-pyridyl-CH_2-, 3-pyridyl-CH_2-, 4-pyridyl-CH_2-, 5-(3-N-methyl)imidazolyl-CH_2-, N-benzylpiperid-4-yl- CH_2-, N-Boc-piperidin-4-yl-CH_2-, N-(phenyl-carbonyl)piperidin-4-yl-CH_2-, $H_3CSCH_2CH_2$-, 1-N-benzylimidazol-4-yl-CH_2-, *iso*-propyl-$C(O)NH$-$(CH_2)_4$-, *iso*-butyl-$C(O)NH$-$(CH_2)_4$-, phenyl-$C(O)NH$-$(CH_2)_4$-, benzyl-$C(O)NH$-$(CH_2)_4$-, allyl-$C(O)NH$-$(CH_2)_4$-, 4-(3-N-methylimidazolyl)-CH_2-, 4-[$(CH_3)_2NCH_2CH_2CH_2$-O-]benzyl, 4-[$(benzyl)_2N$-]-benzyl, 4-aminobenzyl, allyloxy-$C(O)NH(CH_2)_4$-, allyloxy-$C(O)NH(CH_2)_3$-, allyloxy-$C(O)NH(CH_2)_2$-, $NH_2C(O)CH_2$-, ø-CH=, 2-pyridyl-$C(O)NH$-$(CH_2)_4$-, 4-methylpyrid-3-yl-$C(O)NH$-$(CH_2)_4$-, 3-methylthien-2-yl-$C(O)NH$-$(CH_2)_4$-, 2-pyrrolyl-$C(O)NH$-$(CH_2)_4$-, 2-furanyl-$C(O)NH$-$(CH_2)_4$-, 4-methylphenyl-SO_2-$N(CH_3)CH_2C(O)NH(CH_2)_4$-, 4-[cyclopentylacetylenyl]-benzyl, 4-[-NHC(O)-(N-Boc)-pyrrolidin-2-yl)]-benzyl-, 1-N-methylimidazol-4-yl-CH_2-, 1-N-methylimidazol-5-yl-CH_2-, imidazol-5-yl-CH_2, 6-methylpyrid-3-yl-$C(O)NH$-$(CH_2)_4$-, 4-[-$NHC(O)NHCH_2CH_2CH_2$-ø]-benzyl, 4-[-$NHC(O)NHCH_2CH_2$-ø]-benzyl, -$CH_2C(O)NH(CH_2)_4$-ø, 4-[ø $(CH_2)_4O$-]-benzyl, 4-[-C≡ C-4'-ø]-benzyl, 4-[-C≡ C-CH_2-O-$S(O)_2$-4'-CH_3-ø]-benzyl, 4-[-C≡ C-$CH_2NHC(O)NH_2$]-benzyl, 4-[-C≡ C-CH_2-O-4'-$COOCH_2CH_2$-ø]-benzyl, 4-[-C≡ C-CH(NH_2)-cyclohexyl]-benzyl, -$(CH_2)_4NHC(O)CH_2$-3-indolyl, -$(CH_2)_4NHC(O)CH_2CH_2$-3-indolyl, -$(CH_2)_4NHC(O)$-3-(5-methoxyindolyl), -$(CH_2)_4NHC(O)$-3-(1-methylindolyl), -$(CH_2)_4NHC(O)$-4-(-$SO_2(CH_3)$-ø), -$(CH_2)_4NHC(O)$-4-(C(O)CH_3)-phenyl, -$(CH_2)_4NHC(O)$-4-fluorophenyl, -$(CH_2)_4NHC(O)CH_2O$-4-fluorophenyl, 4-[-C≡ C-(2-pyridyl)]-benzyl, 4-[-C≡ C-CH_2-O-phenyl]-benzyl, 4-[-C≡ C-CH_2OCH_3]-benzyl, 4-[-C≡ C-(3-hydroxyphenyl)]-benzyl, 4-[-C≡ C-CH_2-O-4'-(-$C(O)OC_2H_5$)phenyl]-benzyl, 4-[-C≡ C-$CH_2CH(C(O)OCH_3)_2$]-benzyl, 4-[-C≡ C-CH_2NH-(4,5-dihydro-4-oxo-5-phenyl-oxazol-2-yl), 3-aminobenzyl, 4-[-C≡ C-$CH_2CH(NHC(O)CH_3)C(O)OH$]-

benzyl, -$CH_2C(O)NHCH(CH_3)ø$, -$CH_2C(O)NHCH_2$-(4-dimethylamino)-ø, -$CH_2C(O)NHCH_2$-4-nitrophenyl, -$CH_2CH_2C(O)N(CH_3)CH_2$-ø, -$CH_2CH_2C(O)NHCH_2CH_2$-(N-methyl)-2-pyrrolyl, -$CH_2CH_2C(O)NHCH_2CH_2CH_2CH_3$, -$CH_2CH_2C(O)NHCH_2CH_2$-3-indolyl, -$CH_2C(O)N(CH_3)CH_2$phenyl, -$CH_2C(O)NH(CH_2)_2$(N-methyl)-2-pyrrolyl, -$CH_2C(O)NHCH_2CH_2CH_2CH_3$, -$CH_2C(O)NHCH2CH_2$-3-indolyl, -$(CH_2)_2C(O)NHCH(CH_3)ø$, -$(CH_2)_2C(O)NHCH_2$-4-dimethylaminophenyl, -$(CH_2)_2C(O)NHCH_2$-4-nitrophenyl, -$CH_2C(O)$NH-4-[-$NHC(O)CH_3$-phenyl], -$CH_2C(O)$NH-4-pyridyl, -$CH_2C(O)$NH-4-[dimethylaminophenyl], -$CH_2C(O)$NH-3-methoxyphenyl, -$CH_2CH_2C(O)$NH-4-chlorophenyl, -$CH_2CH_2C(O)$NH-2-pyridyl, -$CH_2CH_2C(O)$NH-4-methoxyphenyl, -$CH_2CH_2C(O)$NH-3-pyridyl, 4-[$(CH_3)_2NCH_2CH_2O$-]-benzyl, -$(CH_2)_3NHC(NH)NH$-SO_2-4-methylphenyl, 4-[$(CH_3)_2NCH_2CH_2O$-]-benzyl, -$(CH_2)_4NHC(O)NHCH_2CH_3$, -$(CH_2)_4NHC(O)$NH-phenyl, -$(CH_2)_4NHC(O)$NH-4-methoxyphenyl, 4-[4'-pyridyl-C(O)NH-]-benzyl, 4-[3'-pyridyl-C(O)NH-]-benzyl, 4-[-NHC(O)NH-3'-methylphenyl]-benzyl, 4-[-$NHC(O)CH_2NHC(O)$NH-3'-methylphenyl]-benzyl, 4-[-NHC(O)-(2',3'-dihydroindol-2-yl)]-benzyl, 4-[-NHC(O)-(2',3'-dihydro-N-Boc-indol-2-yl)]-benzyl, p-[-OCH_2CH_2-1'-(4'-pyrimidinyl)-piperazinyl]-benzyl, 4-[-OCH_2CH_2-(1'-piperidinyl)]-benzyl, 4-[-OCH_2CH_2-(1'-pyrrolidinyl)]-benzyl, 4-[-$OCH_2CH_2CH_2$-(1'-piperidinyl)]-benzyl-, -CH_2-3-(1,2,4-triazolyl), 4-[-$OCH_2CH_2CH_2$-4-(3'-chlorophenyl)-piperazin-1-yl]-benzyl, 4-[-OCH_2CH_2N(ø)CH_2CH_3]benzyl, 4-[-OCH_2-3'-(N-Boc)-piperidinyl]-benzyl, 4-[di-*n*-pentylamino]-benzyl, 4-[*n*-pentylamino]-benzyl, 4-[di-*iso*-propylamino-CH_2CH_2O-]-benzyl, 4-[-OCH_2CH_2-(N-morpholinyl)]-benzyl, 4-[-O-(3'-(N-Boc)-piperidinyl]-benzyl, 4-[-OCH_2CH(NHBoc)CH_2cyclohexyl]-benzyl, *p*-[OCH_2CH_2-(N-piperidinyl]-benzyl, 4-[-$OCH_2CH_2CH_2$-(4-*m*-chlorophenyl)-piperazin-1-yl]-benzyl, 4-[-OCH_2CH_2-(N-homopiperidinyl)-benzyl, 4-[-NHC(O)-3'-(N-Boc)-piperidinyl]-benzyl, 4-[-OCH_2CH_2N(benzyl)$_2$]-benzyl, -CH_2-2-thiazolyl, 3-hydroxybenzyl, 4-[-$OCH_2CH_2CH_2N(CH_3)_2$]-benzyl, 4-[-NHC(S)$NHCH_2CH_2$-(N-morpholino)]-benzyl, 4-[-$OCH_2CH_2N(C_2H_5)_2$]-benzyl, 4-[-$OCH_2CH_2CH_2N(C_2H_5)_2$]-benzyl, 4-[$CH_3(CH_2)_4NH$-]-benzyl, 4-[N-*n*-butyl,N-*n*-pentylamino-

]benzyl, 4-[-NHC(O)-4'-piperidinyl]benzyl, 4-[-NHC(O)CH(NHBoc)$(CH_2)_4$NHCbz]-benzyl, 4-[-NHC(O)-(1',2',3',4'-tetrahydro-N-Boc-isoquinolin-1'-yl]-benzyl, p-[-$OCH_2CH_2CH_2$-1'-(4'-methyl)-piperazinyl]-benzyl, -$(CH_2)_4$NH-Boc, 3-[-$OCH_2CH_2CH_2N(CH_3)_2$]-benzyl, 4-[-$OCH_2CH_2CH_2N(CH_3)_2$]-benzyl, 3-[-OCH_2CH_2-(1'-pyrrolidinyl)]-benzyl, 4-[-$OCH_2CH_2CH_2N(CH_3)$benzyl]-benzyl, 4-[-NHC(S)$NHCH_2CH_2CH_2$-(N-morpholino)]-benzyl, 4-[-OCH_2CH_2-(N-morpholino)]-benzyl, 4-[-$NHCH_2$-(4'-chlorophenyl)]-benzyl, 4-[-NHC(O)NH-(4'-cyanophenyl)]-benzyl, 4-[-OCH_2COOH]-benzyl, 4-[-OCH_2COO-*t*-butyl]-benzyl, 4-[-NHC(O)-5'-fluoroindol-2-yl]-benzyl, 4-[-NHC(S)$NH(CH_2)_2$-1-piperidinyl]-benzyl, 4-[-$N(SO_2CH_3)(CH_2)_3$-$N(CH_3)_2$]-benzyl, 4-[-NHC(O)CH_2CH(C(O)OCH_2ø)-NHCbz]-benzyl, 4-[-$NHS(O)_2$-CF_3]-benzyl, 3-[-O-(N-methylpiperidin-4'-yl]-benzyl, 4-[-C(=NH)NH_2]-benzyl, 4-[-$NHSO_2$-CH_2C1]-benzyl, 4-[-NHC(O)-(1',2',3',4'-tetrahydroisoquinolin-2'-yl]-benzyl, 4-[-NHC(S)$NH(CH_2)_3$-N-morpholino]-benzyl, 4-[-NHC(O)$CH(CH_2CH_2CH_2CH_2NH_2)$NHBoc]-benzyl, 4-[-C(O)NH_2]-benzyl, 4-[-NHC(O)NH-3'-methoxyphenyl]-benzyl, 4-[-OCH_2CH_2-indol-3'-yl]-benzyl, 4-[-OCH_2C(O)NH-benzyl]-benzyl, 4-[-OCH_2C(O)O-benzyl]-benzyl, 4-[-OCH_2C(O)OH]-benzyl, 4-[-OCH_2-2'-(4',5'-dihydro)imidazolyl]-benzyl, -CH_2C(O)$NHCH_2$-(4-dimethylamino)phenyl, -CH_2C(O)$NHCH_2$-(4-dimethylamino)phenyl, 4-[-NHC(O)-L-2'-pyrrolidinyl-N-SO_2-4'-methylphenyl]-benzyl, 4-[-NHC(O)$NHCH_2CH_2CH_3$]-benzyl, [4-aminobenzyl]-benzyl, 4-[-OCH_2CH_2-1-(4-hydroxy-4-(3-methoxypyrrol-2-yl)-piperazinyl]-benzyl, 4-[-O-(N-methylpiperidin-4'-yl)]-benzyl, 3-methoxybenzyl, 4-[-NHC(O)-piperidin-3'-yl]-benzyl, 4-[-NHC(O)-pyridin-2'-yl]-benzyl, 4-[-$NHCH_2$-(4'-chlorophenyl)]-benzyl, 4-[-NHC(O)-(N-(4'-CH3-ø-SO_2)-L-pyrrolidin-2'-yl)]-benzyl, 4-[-NHC(O)$NHCH_2CH_2$-ø]-benzyl, 4-[-OCH_2C(O)NH_2]-benzyl, 4-[-OCH_2C(O)NH-*t*-butyl]-benzyl, 4-[-OCH_2CH_2-1-(4-hydroxy-4-phenyl)-piperidinyl]-benzyl, 4-[-$NHSO_2$-CH=CH_2]-benzyl, 4-[-$NHSO_2$-CH_2CH_2C1]-benzyl, -CH_2C(O)$NHCH_2CH_2N(CH_3)_2$, 4-[(1'-Cbz-piperidin-4'-yl)C(O)NH-]benzyl, 4-[(1'-Boc-piperidin-4'-yl)C(O)NH-]benzyl, 4-[(2'-bromophenyl)C(O)NH-]benzyl, 4-[-NHC(O)-pyridin-4'-yl]-benzyl, 4-[(4'-$(CH_3)_2NC$(O)O-)phenyl)-C(O)NH-]benzyl,

4-[-NHC(O)-1'-methylpiperidin-4'-yl-]benzyl, 4-(dimethylamino)benzyl, 4-[-NHC(O)-(1'-N-Boc)-piperidin-2'-yl]-benzyl, 3-[-NHC(O)-pyridin-4'-yl]-benzyl, 4-[(*tert*-butyl-O(O)CCH$_2$-O-benzyl)-NH-]benzyl, [BocNHCH$_2$C(O)NH-]butyl, 4-benzyl-benzyl, 2-hydroxyethyl, 4-[(Et)$_2$NCH$_2$CH$_2$CH$_2$NHC(S)NH-]benzyl, 4-[(1'-Boc-4'-hydroxypyrrolidin-2'-yl)C(O)NH-]benzyl, 4-[øCH$_2$CH$_2$CH$_2$NHC(S)NH-]benzyl, 4-[(perhydroindolin-2'-yl)C(O)NH-]benzyl, 2-[4-hydroxy-4-(3-methoxythien-2-yl)piperidin-1-yl]ethyl, 4-[(1'-Boc-perhydroindolin-2'-yl)-C(O)NH-]benzyl, 4-[*N*-3-methylbutyl-*N*-trifluoromethanesulfonyl)amino]-benzyl, 4-[*N*-vinylsulfonyl)amino]benzyl-, 4-[2-(2-azabicyclo[3.2.2]octan-2-yl)ethyl-O-]benzyl, 4-[4'-hydroxypyrrolidin-2'-yl)C(O)NH-]benzyl, 4-(øNHC(S)NH)benzyl, 4-(EtNHC(S)NH)benzyl,4-(øCH$_2$NHC(S)NH)benzyl, 3-[(1'-Boc-piperidin-2'-yl)C(O)NH-]benzyl, 3-[piperidin-2'-yl-C(O)NH-]benzyl, 4-[(3'-Boc-thiazolidin-4'-yl)C(O)NH-]benzyl, 4-(pyridin-3'-yl-NHC(S)NH)benzyl, 4-(CH$_3$-NHC(S)NH)benzyl-, 4-(H$_2$NCH$_2$CH$_2$CH$_2$C(O)NH)benzyl, 4-(BocHNCH$_2$CH$_2$CH$_2$C(O)NH)benzyl, 4-(pyridin-4'-yl-CH$_2$NH)benzyl, 4-[(*N,N*-di(4-*N,N*-dimethylamino)benzyl)amino]benzyl, 4-[(1-Cbz-piperidin-4-yl)C(O)NH-]butyl, 4-[øCH$_2$OCH$_2$(BocHN)CHC(O)NH]benzyl, 4-[(piperidin-4'-yl)C(O)NH-]benzyl, 4-[(pyrrolidin-2'-yl)C(O)NH-]benzyl, 4-(pyridin-3'-yl-C(O)NH)butyl, 4-(pyridin-4'-yl-C(O)NH)butyl, 4-(pyridin-3'-yl-C(O)NH)benzyl, 4-[CH$_3$NHCH$_2$CH$_2$CH$_2$C(O)NH-]benzyl, 4-[CH$_3$N(Boc)CH$_2$CH$_2$CH$_2$C(O)NH-]benzyl, 4-(aminomethyl)benzyl, 4-[øCH$_2$OCH$_2$(H$_2$N)CHC(O)NH]benzyl, 4-[(1',4'-di(Boc)piperazin-2'-yl)-C(O)NH-]benzyl, 4-[(piperazin-2'-yl)-C(O)NH-]benzyl, 4-[(*N*-toluenesulfonylpyrrolidin-2'-yl)C(O)NH-]butyl, 4-[-NHC(O)-4'-piperidinyl]butyl, 4-[-NHC(O)-1'-N-Boc-piperidin-2'-yl]-benzyl, 4-[-NHC(O)-piperidin-2'-yl]-benzyl, 4-[(1'-N-Boc-2',3'-dihydroindolin-2'-yl)-C(O)NH]-benzyl, 4-(pyridin-3'-yl-CH$_2$NH)benzyl, 4-[(1'-Cbz-piperidin-4'-yl)C(O)NH-]benzyl, 4-[(piperidin-1'-yl)C(O)CH$_2$-O-]benzyl, 4-[(CH$_3$)$_2$CH)$_2$NC(O)CH$_2$-O-]benzyl, 4-[HO(O)C(Cbz-NH)CHCH$_2$CH$_2$-C(O)NH-]benzyl, 4-[øCH$_2$O(O)C(Cbz-NH)CHCH$_2$CH$_2$-C(O)NH-]benzyl, 4-[-NHC(O)-2'-methoxyphenyl]-benzyl, 4-[(pyrazin-2'-yl)C(O)NH-]benzyl, 4-[HO(O)C(NH$_2$)CHCH$_2$CH$_2$-C(O)NH-]benzyl, 4-(2'-formyl-

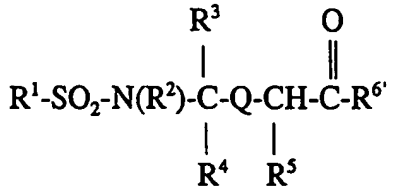
1',2',3',4'-tetrahydroisoquinolin-3'-yl-CH_2NH-)benzyl, *N*-Cbz-$NHCH_2$-, 4-[(4'-methylpiperazin-1'-yl)C(O)O-]benzyl, 4-[CH_3(*N*-Boc)$NCH_2C(O)NH$-]benzyl, 4-[-NHC(O)-(1',2',3',4'-tetrahydro-N-Boc-isoquinolin-3'-yl]-benzyl, 4-[$CH_3NHCH_2C(O)NH$-]benzyl, $(CH_3)_2NC(O)CH_2$, 4-(*N*-methylacetamido)benzyl, 4-(1',2',3',4'-tetrahydroisoquinolin-3'-yl-CH_2NH-)benzyl, 4-[$(CH_3)_2NHCH_2C(O)NH$-]benzyl, (1-toluenesulfonylimidizol-4-yl)methyl, 4-[(1'-Boc-piperidin-4'-yl)C(O)NH-]benzyl, 4-trifluoromethylbenzyl, 4-[(2'-bromophenyl)C(O)NH-]benzyl, 4-[$(CH_3)_2NC(O)NH$-]benzyl, 4-[$CH_3OC(O)NH$-]benzyl, 4-[$(CH_3)_2NC(O)O$-]benzyl, 4-[$(CH_3)_2NC(O)N(CH_3)$-]benzyl, 4-[$CH_3OC(O)N(CH_3)$-]benzyl, 4-(*N*-methyltrifluoroacetamido)benzyl, 4-[(1'-methoxycarbonylpiperidin-4'-yl)C(O)NH-]benzyl, 4-[(4'-phenylpiperidin-4'-yl)C(O)NH-]benzyl, 4-[(4'-phenyl-1'-Boc-piperidin-4'-yl)-C(O)NH-]benzyl, 4-[(piperidin-4'-yl)C(O)O-]benzyl, 4-[(1'-methylpiperadin-4'-yl)-O-]benzyl, 4-[(1'-methylpiperidin-4'-yl)C(O)O-]benzyl, 4-[(4'-methylpiperazin-1'-yl)C(O)NH-]benzyl, 3-[$(CH_3)_2NC(O)O$-]benzyl, 4-[(4'-phenyl-1'-Boc-piperidin-4'-yl)-C(O)O-]benzyl, 4-(*N*-toluenesulfonylamino)benzyl, 4-[$(CH_3)_3CC(O)NH$-]benzyl, 4-[(morpholin-4'-yl)C(O)NH-]benzyl, 4-[$(CH_3CH_2)_2NC(O)NH$-]benzyl, 4-[-C(O)NH-(4'-piperidinyl)]benzyl, 4-[(2'-trifluoromethylphenyl)C(O)NH-]benzyl, 4-[(2'-methylphenyl)C(O)NH-]benzyl, 4-[$(CH_3)_2NS(O)_2$-O-]benzyl, 4-[(pyrrolidin-2'-yl)C(O)NH-]benzyl, 4-[-NHC(O)-piperidin-1'-yl]benzyl, 4-[(thiomorpholin-4'-yl)C(O)NH-]benzyl, 4-[(thiomorpholin-4'-yl sulfone)-C(O)NH-]benzyl, 4-[(morpholin-4'-yl)C(O)O-]benzyl, 3-nitro-4-($CH_3OC(O)CH_2O$-)benzyl, (2-benzoxazolinon-6-yl)methyl-, (2*H*-1,4-benzoxazin-3(4*H*)-one-7-yl)methyl-, 4-[$(CH_3)_2NS(O)_2NH$-]benzyl, 4-[$(CH_3)_2NS(O)_2N(CH_3)$-]benzyl, 4-[(thiomorpholin-4'-yl)C(O)O-]benzyl, 4-[(thiomorpholin-4'-yl sulfone)-C(O)O-]benzyl, 4-[(piperidin-l'-yl)C(O)O-]benzyl, 4-[(pyrrolidin-1'-yl)C(O)O-]benzyl, 4-[(4'-methylpiperazin-1'-yl)C(O)O-]benzyl, 4-[(2'-methylpyrrolidin-1'-yl)-, (pyridine-4-yl)methyl-, 4-[(piperazin-4'-yl)-C(O)O-]benzyl, 4-[(1'-Boc-piperazin-4'-yl)-C(O)O-]benzyl, 4-[(4'-acetylpiperazin-1'-yl)C(O)O-]benzyl, *p*-[(4'-methanesulfonylpiperazin-1'-yl)-benzyl, 3-nitro-4-[(morpholin-4'-yl)-C(O)O-]benzyl,

4-{[$(CH_3)_2NC(S)]_2N$-}benzyl, *N*-Boc-2-aminoethyl-, 4-[(1,1-dioxothiomorpholin-4-yl)-C(O)O-]benzyl, 4-[$(CH_3)_2NS(O)_2$-]benzyl, 4-[(piperidin-1'-yl)C(O)O-]benzyl, 1-N-benzyl-imidazol-4-yl-CH_2-, 3,4-dioxyethylenebenzyl, 3,4-dioxymethylenebenzyl, 4-[-$N(SO_2)(CH_3)CH_2CH_2CH_2N(CH_3)_2$]benzyl, 4-[$NHC(O)CH(CH_2CH_2CH_2CH_2NH_2)NHBoc$]-benzyl, [2'-[4"-hydroxy-4"-(3'"-methoxythien-2'"-yl)piperidin-2"-yl]ethoxy]benzyl, and p-[$(CH_3)_2NCH_2CH_2N(CH_3)C(O)O$-]benzyl.

13. (Original): The compound according to Claim 2 wherein R^6 is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), methoxy, ethoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, cyclopentoxy, *neo*-pentoxy, 2-α-*iso*-propyl-4-β-methylcyclohexoxy, 2-β-isopropyl-4-β-methylcyclohexoxy, - NH_2, benzyloxy, $-NHCH_2COOH$, $-NHCH_2CH_2COOH$, -NH-adamantyl, $-NHCH_2CH_2COOCH_2CH_3$, -NHSO2-*p*-CH_3ø), $-NHOR^8$ where R^8 is hydrogen, methyl, *iso*-propyl or benzyl, O-(N-succinimidyl), -O-cholest-5-en-3-β-yl, $-OCH_2$-$OC(O)C(CH_3)_3$, $-O(CH_2)_zNHC(O)W$ where *z* is 1 or 2 and W is selected from the group consisting of pyrid-3-yl, N-methylpyridyl, and N-methyl-1,4-dihydro-pyrid-3-yl, -NR"C(O)-R' where R' is aryl, heteroaryl or heterocyclic and R" is hydrogen or $-CH_2C(O)OCH_2CH_3$.

15. (Original): A method for binding VLA-4 in a biological sample which method comprises contacting the biological sample with a compound of Claims 1 or 2 under conditions wherein said compound binds to VLA-4.

16. (Four times amended): A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the formula:



where

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a heterocyclic or a substituted heterocyclic group selected from the group consisting of thiazolidinyl, piperidinyl and pyrrolidinyl wherein said substituted heterocyclic group consists of from 1 to 2 substituents selected from the group consisting of fluoro, methyl, hydroxyl, amino, phenyl, thiophenyl and thiobenzyl;

R^4 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^5 is selected from the group consisting of isopropyl, $-CH_2X$ and $=CH-X$ where X is selected from the group consisting of:

hydrogen,

hydroxyl,

acylamino,

alkyl,

alkoxy,

aryloxy,

aryl,

aryloxyaryl,

carboxyl,

carboxylalkyl,

carboxyl-substituted alkyl,

carboxyl-cycloalkyl,

carboxyl-substituted cycloalkyl,

carboxylaryl,

carboxyl-substituted aryl,

carboxylheteroaryl,

carboxyl-substituted heteroaryl,

carboxylheterocyclic,

carboxyl-substituted heterocyclic,

cycloalkyl,

substituted alkyl

substituted alkoxy,

substituted aryl,

substituted aryloxy,

substituted aryloxyaryl,

substituted cycloalkyl,

heteroaryl,

substituted heteroaryl,

heterocyclic,

and substituted heterocyclic;

wherein substituted aryl refers to aryl groups substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy,

aminocarbonylamino, aminothiocarbonylamino, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heterocyclic, substituted heterocyclic, oxycarbonylamino, oxythiocarbonylamino, $-S(O)_2$-alkyl, $-S(O)_2$-substituted alkyl, $-S(O)_2$- cycloalkyl, $-S(O)_2$-substituted cycloalkyl, $-S(O)_2$-alkenyl, $-S(O)_2$-substituted alkenyl, $-S(O)_2$-aryl, $-S(O)_2$-substituted aryl, $-S(O)_2$-heteroaryl, $-S(O)_2$-substituted heteroaryl, $-S(O)_2$-heterocyclic, $-S(O)_2$-substituted heterocyclic, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where R is hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$- NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking

groups selected from the group consisting of Boc, Cbz, and formyl or substituted with $-SO_2NRR$ where R is hydrogen or alkyl; and

substituted heteroaryl refers to heteroaryl groups substituted with from 1 to 3 substituents selected of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heterocyclic, substituted heterocyclic, oxycarbonylamino, oxythiocarbonylamino, $-S(O)_2$-alkyl, $-S(O)_2$-substituted alkyl, $-S(O)_2$- cycloalkyl, $-S(O)_2$-substituted cycloalkyl, $-S(O)_2$-alkenyl, $-S(O)_2$-substituted alkenyl, $-S(O)_2$-aryl, $-S(O)_2$-substituted aryl, $-S(O)_2$-heteroaryl, $-S(O)_2$-substituted heteroaryl, $-S(O)_2$-heterocyclic, $-S(O)_2$-substituted heterocyclic, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2NRR$ where R is hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$- substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$- NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and

di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups selected from the group consisting of Boc, Cbz, and formyl or substituted with $-SO_2NRR$ where R is hydrogen or alkyl;

with the proviso that when R^5 is =CH-X then (H) is removed from the formula and X is not hydroxyl;

$R^{6'}$ is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), hydroxyl, amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, or substituted aryl, $-NH(CH_2)_pCOOY$ where *p* is an integer of from 1 to 8 and Y is as defined above, $-OCH_2NR^9R^{10}$ where R^9 is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and R^{10} is selected from the group consisting of hydrogen and $-CH_2COOR^{11}$ where R^{11} is alkyl, and $-NHSO_2Z$ where Z is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

Q is $-C(X')NR^7-$ wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

or pharmaceutically acceptable salts thereof

with the proviso that

when R^1 is *p*-methylphenyl, R^2 and R^3 are joined together with the nitrogen atom pendent to R^2 and the carbon atom pendent to R^3 to form a pyrrolidinyl ring, R^4 is methyl, R^5 is *p*-hydroxybenzyl then $R^{6'}$ is not *t*-butoxy.

17. (Original): A method for the treatment of an inflammatory disease in a patient mediated by VLA-4 which methods comprise administering to the patient the pharmaceutical composition of Claim 16.

18. (Twice amended): The method according to Claim 17 wherein said inflammatory disease is selected from the group consisting of asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury which occurs in adult respiratory distress syndrome.

19. (Previously presented): The method according to Claim 18 wherein said diabetes is acute juvenile onset diabetes.

20. (Previously presented): The method according to Claim 18 wherein said inflammatory bowel disease is ulcerative colitis or Crohn's disease.

21. (Previously presented): The method according to Claim 18 wherein said cerebral trauma is stroke.

22. (Once amended): A compound selected from the group consisting of:

N-(toluene-4-sulfonyl)-L-α-methylprolyl-L-phenylalanine;

N-(toluene-4-sulfonyl)-L-α-methylprolyl-L-4-(isonicotinamido)phenylalanine methyl ester;

N-(toluene-4-sulfonyl)-L-α-methylprolyl-L-4-(isonicotinamido)phenylalanine;

N-(toluene-4-sulfonyl)-α-methylprolyl-L-4-(1-methylpiperidin-4-oxy)phenylalanine ethyl ester;

N-(toluene-4-sulfonyl)-α-methylprolyl-L-4-(1-methylpiperidin-4-oxy)phenylalanine;

N-(toluene-4-sulfonyl)-α-methylprolyl-L-4-(4-methylpiperazin-l-carbonyloxy)phenyl-alanine *tert*-butyl ester;

N-(toluene-4-sulfonyl)-α-methylprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester;

N-(toluene-4-sulfonyl)-α-methylprolyl-L-4-(4-methylpiperazin-1-carbonyloxy)phenyl-alanine;

N-(toluene-4-sulfonyl)-α-methylprolyl-L-tyrosine *tert*-butyl ester;

N-(toluene-4-sulfonyl)-α-methylprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine;

N-(toluene-4-sulfonyl)-α-methylprolyl-L-4-(morpholin-4-ylcarbonyloxy)phenyl-alanine *tert*-butyl ester;

N-(toluene-4-sulfonyl)-α-methylprolyl-L-4-(morpholin-4-ylcarbonyloxy)phenyl-alanine;

N-(toluene-4-sulfonyl)-α-methylprolyl-D-tyrosine *tert*-butyl ester;

N-(toluene-4-sulfonyl)-α-methylprolyl-L-4-(morpholin-4-ylcarbonyloxy)phenyl-alanine 1-(trimethyacetoxy)methyl ester;

N-(toluene-4-sulfonyl)-α-methylprolyl-L-4-[N-(2-(N',N'-dimethylamino)ethyl)-N-methylcarbamyloxy]phenylalanine *tert*-butyl ester;

N-(toluene-4-sulfonyl)-α-methylprolyl-L-4-[N-(2-(N',N'-dimethylamino)ethyl)-N-methylcarbamyloxy]phenylalanine;

N-(4-fluorobenzenesulfonyl)-α-methylprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester;

N-(4-fluorobenzenesulfonyl)-α-methylprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenyl-alanine

or pharmaceutically acceptable salts thereof or any of the ester compounds recited above wherein one ester group is replaced with another ester group selected from the group consisting of methyl ester, ethyl ester, *n*-propyl ester, isopropyl ester, *n*-butyl ester, isobutyl ester, *sec*-butyl ester and *tert*-butyl ester.

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In re COES

(CCPA)
81 USPQ 369
Decided Apr. 12, 1949
Appl. No. 5555
U.S. Court of Customs and Patent Appeals

Headnotes

PATENTS

1. Patentability -- Invention -- Specific cases
Where prior art teaches use of aldehydes and ethers, it is not invention to select particular kind of ether derived from dehydration of alcohols (the dehydration of which is the common source of ether) and aldehydes.

2. Patentability -- Invention -- Specific cases
Adjacent homologues of old substances are unpatentable as new compounds particularly where homologues are not markedly superior to old substances.

Particular patents--Abrasive
Coes, Abrasive Articles and Method of Making the Same, claims 1 and 2 of application refused.

Case History and Disposition:

Appeal from Board of Appeals of the Patent Office.
Application for patent of Loring Coes, Jr., Serial No. 529,175; Patent

Office Division 58. From decision rejecting claims 1 to 4, applicant appeals. Affirmed as to claims 1 and 2; appeal dismissed as to claims 3 and 4.

Attorneys:

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W. W. COCHRAN (CLARENCE W. MOORE of counsel) for Commissioner of Patents.

Opinion Text

Opinion By:

JOHNSON, Judge.

This is an appeal from the decision of the Board of Appeals of the United States Patent Office affirming the examiner's rejection of claims 1 to 4, inclusive, of appellant's application for a patent entitled "Abrasive Articles and Method of Making the Same." The rejection was based on prior art, the references cited being the following patents:

Martin, Re. 19,318, Sept. 18, 1934.
Kistler, 2,272,873, Feb. 10, 1942.
Kistler, 2,272,874, Feb. 10, 1942.
Kistler, 2,272,875, Feb. 10, 1942.
Coes, 2,309,575, Jan. 26, 1943.

In accordance with the motion filed by appellant at the oral argument, the appeal will be dismissed as to claims 3 and 4.

Claims 1 and 2 read as follows:

1. The method of making a grinding wheel or other abrasive body comprising wetting abrasive grain with a grain-wettant and resin-hardening agent selected from the group consisting of di-2-chlorethyl formal, di-2-chlorethyl benzal, di-2-chlorethyl enanthal, di-2-chlorethyl propanal, di-2-chlorethyl furfural and di-2-chlorethyl butyral, mixing therewith primary aromatic amine formaldehyde resin and thereby producing a dry granular mix, and shaping and heat-treating the mix.

2. A grinding wheel or other abrasive body comprising abrasive grains bonded with the reaction product under heat treatment of primary aromatic amine formaldehyde resin and a grain-wetting and resin-hardening agent selected from the group consisting of di-2-chlorethyl formal, di-2-chlorethyl benzal, di-2-chlorethyl enanthal, di-2-chlorethyl propanal, di-2-chorethyl furfural and di-2-

chlorethyl butyral.

The appealed claims relate to a grinding wheel comprising abrasive grains, an aniline-formaledhyde resin, and a resin hardening agent, illustrated by di-2-chlorethyl formal. It is claimed that the last mentioned reagent also possesses grain-wetting properties, and may be replaced by named derivatives thereof.

Appellant claims that his application here involved provides for the use of compounds which are all acetals, and that the patent to Coes, 2,309,575, provides for the use of compounds which are ethers, and that "nothing in the appellant's prior patent No. 2,309,575 is a homologue of any of the resin hardening agents specified in the claims of the application on appeal."

The examiner rejected the claims here involved on the ground that the ether covered by appellant's patent, No. 2,309,575, supra, and the formal specified in the claims of the application are adjacent members of the same homologous series, and that the patent discloses the next higher homologue of the claimed formal.

The Board of Appeals in its decision said:

> In our opinion, the issue is not the technical one of whether appellant's compound and that of the patent are strictly homologues but rather whether they are to be considered so closely related that the teaching of one might suggest the other and whether the substitution leads to obvious results. We are of the opinion that the compounds are closely related, and that chemists recognize this close relationship and therefore that the teaching of one would suggest the other.

The Martin patent, Reissue No. 19,318, supra, teaches the use of furfural, which is an aldehyde, as the coating solvent for producing abrasive articles.

The Kistler patents, 2,272,873-4-5, each teach the use of an aldehyde and remote halogen containing compounds as hardening agents in producing grinding wheels and other abrasive bodies.

The patent to Coes, 2,309,575, supra, teaches the use of aldehydes in making grinding wheels, etc., and describes a grinding wheel composition which differs from that claimed here only in the hardening agent.

It was the board's opinion that the most nearly related hardening agent of the reference (Coes patent, 2,309,575, supra) is triglycol dichloride, which may be represented as:

$$Cl -- CH_2 -- CH_2 -- O -- CH_2 -- CH_2 -- O -- CH_2 -- CH_2 -- Cl$$

Appellant's illustrative reagent may be represented as:

$$Cl -- CH_2 -- CH_2 -- O -- CH_2 -- O -- CH_2 -- CH_2 -- Cl.$$

Appellant contends that the reagent of his application is not a homologue of the hardening agent of his cited patent; that triglycol dichloride is an ether, while the hardening agents of his application are acetals; that acetals and ethers are recognized as different in the field of chemistry; that in selecting di-2-chlorethyl formal for use as a resin hardening agent, he secured an unobvious and unexpected result.

Bearing in mind that the prior art discloses the use of aldehydes (Kistler references) and ethers (Coes reference) as hardening agents in producing abrasive bodies, we think the following excerpts from the texts indicated are of interest:

> (From Organic Chemistry, by Paul Karrer, Third English Edition, Elsevier Publishing Co. Inc., Amsterdam, in 1947)

(At page 153). The aldehydes react with alcohols in the presence of small quantities of anhydrous mineral acids of toluene sulphonic acid forming *acetals.* These are the alkyl ethers of the aldehyde hydrates. They are quite stable with respect to alkalis, but they are readily hydrolysed by aqueous mineral acids to the aldehydes. They have a pleasant flower-like smell.

(At page 113). Properties. The ethers are pleasant (ethereal) smelling liquids * * *.

The ethers are very stable substances, more so than the alcohols. They do not react with the alkali metals, * * *. They are very little attacked by alkalies. On the other hand they are easily decomposed by acids, * * *.

(At page 23). * * *. Compounds which have similar chemical and physical properties and which differ in composition by CH_2, or some multiple of it, are called homologous compounds.

(From Theoretical Organic Chemistry, by Julius B. Cohen, MacMillan and Co., Ltd., St. Martin's St., London, 1934)

Page 371

(At page 50). Classification based on Composition and Properties.--If we adopt a system of classification based on composition and properties, we find that there are a number of families of compounds, each member of a family behaving towards reagents in a very similar manner to that of the other members. * * *

(At page 51). Homologous Series.--It will be further observed that each member of a family differs from that which precedes or follows it by the same number of carbon and hydrogen atoms, viz. CH_2. * * * It is only necesary at present to state that families which fulfill the conditions just set forth were named by Gerhardt *homologous series.* A homologous series may therefore be defined as a family of chemically related compounds, the composition of which varies from member to member by one atom of carbon and two atoms of hydrogen. * * *

(From Chambers's Technical Dictionary, The MacMillan Co., New York, 1940)

(At page 6). acetals (Chem.). The dehydration products of aldehydes, with an excess of alcohols present. Acetals may be termed dialkyl ethers of the dihydrates.

(From Hackh's Chemical Dictionary, P. Blakiston's Son & Co. Inc., Philadelphia, 1929)

(At page 5). acetals. A group of organic ethers of the type, R -- CH (OR) 2·

Acetals are formed by the dehydration of alcohols and aldehydes, and ethers are formed by the dehydration of alcohol. The authorities quoted establish acetals as members of the family of ethers. It may be seen from the excerpts from Karrer, supra, that acetals and ethers have similar chemical properties (stable with respect to alkalis, but readily decomposed by acids) as well as a similar physical property (pleasant smelling). It will be observed that the chemical formula for the acetal in issue (di-2-chlorethyl formal) differs from that of the ether disclosed in appellant's prior patent (triglycol dichloride)

only by CH 2. The two compounds have similar chemical and physical properties. They differ in composition by CH 2. The conclusion seems unavoidable that they are, in accordance with the authorities hereinbefore quoted, members of a homologous series.

[1] Where the prior art teaches the use of aldehydes and ethers, is it an advance over the art for an applicant to select a particular kind of ether which is derived from the dehydration of alcohols (the dehydration of which is the common source of ether) *and* aldehydes? Were the answer to be in doubt, it would, as in the instant case, be resolved against the applicant when it appears that the alcohol-aldehyde dehydrate selected differs from a compound known to the art merely by a difference of CH 2in the composition under circumstances persuasive that the elected compound is but a homologue of a compound old in the art.

The case of In re Jones, 32 C.C.P.A. (Patents) 1020, 149 F.2d 501, 65 USPQ 480 , cited by appellant, is clearly distinguishable from the instant case. The Jones case relates to compositions of matter used as insecticides, fungicides, and growth regulants for plants. There the prior art compound and the compound claimed differed in composition, not by CH 2, but by C 4H 2, and under the definitions of homologous compounds cited therein (very similar to those quoted herein), the court considered that disparity partly controlling in its finding that the compound there in issue was not a homologue of the compound known to the art.

Appellant contends that the use of the claimed matter results in a more useful grinding wheel in some regards than has previously been obtained in the art, and specifically that the abrasive wheel which can be produced by the teaching of his application will wear longer than that made available by his patent. In view of the high rate of consumption of grinding wheels in an industrial plant, appellant asserts the new wheel is a "significant" contribution to the art. The solicitor points out that the wheel of the patent removes more metal per unit of time than the new wheel (as revealed by test results cited below by appellant). and the old wheel is superior to the new, viewed from that aspect of efficiency.

[2] We agree with the board that the improvement, if any, is one of degree viewed only from a single aspect. Adjacent homologues of old substances are unpatentable as new compounds particularly where the homologues are not markedly superior to the old substances. Ellis on Patent Claims, sec. 365.

The appeal as to claims 3 and 4 is dismissed, and the decision of the Board of Appeals as to claims 1 and 2 is affirmed.

- End of Case -